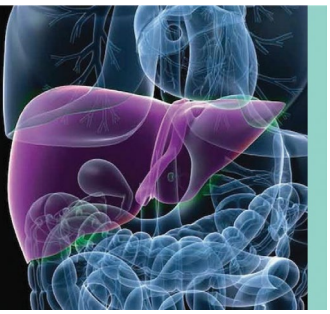

Liver Injury from Herbal and Dietary Supplements: An Introduction

Victor Navarro, M.D.

Hepatotoxicity is a form of liver cell injury resulting from multitude of causes, including drugs, toxins, herbal and dietary supplements (HDSs), and other agents. The goal of the American Association for the Study of Liver Diseases (AASLD) Hepatotoxicity Special Interest Group (SIG) is to promote and encourage research, education, and awareness regarding human hepatotoxicity (https://www.aasld.org/membership/member-resources/special-interest-groups/hepatotoxicity).

The AASLD Hepatotoxicity SIG presented a program for The Liver Meeting 2018 chaired by Victor Navarro and Adrian Reuben. Excerpts of this program have been included in this issue of CLD.[1,2]

HDS–INDUCED LIVER INJURY: DEFINING THE FUTURE

HDSs are commonly used in the United States, often in combination or as multi-ingredient products. Providers may not be aware of a patient's use of supplements, because he or she may not ascertain a history of supplement use or the patient may not report use. In addition, current regulation in the United States is not built to assure the safety of HDSs. The Dietary Supplement Health and Education Act of 1994 serves as the main regulatory framework for HDSs; an excellent summary of the Act can be found on the US Food and Drug Administration Web site (https://www.fda.gov/Food/DietarySupplements/). Specifically, the Act defines the components of supplements (i.e., dietary ingredients) as vitamins, minerals, herbs, or amino acids (and any concentrate, metabolite, or extract thereof). Further, the Act requires supplement manufacturers to attest to the safety of their products, but there is no compulsion to prove safety or efficacy. Manufacturers are held to regulatory standards to assure product purity, strength, and composition; however, adherence to these standards is weakly enforced, and dietary supplements are vulnerable to the inclusion of unlabeled ingredients.

Cases of harm caused by HDSs, particularly liver injury, capture the attention of the media. Yet, despite many highly publicized cases, instances of injury continue to occur. Severe liver injury due to HDSs is a well-documented phenomenon. In the experience of the US Acute

Abbreviations: AASLD, American Association for the Study of Liver Diseases; DILIN, Drug-Induced Liver Injury Network; GTE, green tea extract; HDS, herbal and dietary supplement; SIG, Special Interest Group.

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Liver Failure Study group, drugs and HDSs were the second most common cause of acute liver failure, with acetaminophen being the most common.[3] A closer analysis of cases from this group revealed that the proportion of cases due to HDSs relative to prescription drugs has been increasing.[4]

HDSs can be implicated as a cause for liver injury only after a careful process to exclude other causes, including viral hepatitis and anatomic, hemodynamic, autoimmune, and metabolic diseases. Such an approach serves as the foundation for structured approaches to assign the likelihood of liver injury caused by an agent. In the Drug-Induced Liver Injury Network (DILIN), this structured approach is supplemented with expert opinion.

The US DILIN has added much information to the understanding of liver injury caused by HDSs. Here again, HDSs are a common cause of liver injury, superseded as a cause only by antimicrobials. The frequency of cases in the DILIN caused by HDSs has remained stable at about 20% of the total, with non-body-building products being a more frequent cause of injury than body-building products. The outcomes of liver injury caused by HDSs can be severe; in fact, liver injury from non-body-building products are more likely to lead to liver transplantation than other types of products or prescription medications.[5]

Many cases of liver injury caused by HDS have been documented in the literature, leaving little doubt as to the potential for harm. The precise cause for injury often is unclear; that is, whether it is due to a single ingredient or combination thereof, an adulterant, or something unrelated to the product often cannot be pinpointed. Still, the DILIN has focused its resources on the products that have been retrieved from patients who sustained injury, in whom the likelihood of injury was thought to be due to the product. In its analysis of the implicated products, it was found that 51% of products had inaccurate labels.[6] In a few cases, an unlabeled ingredient that was identified through high-performance liquid chromatography was strongly suspected to be the cause for injury based on a pattern of injury previously associated with the ingredient and no other cause.

Green tea extract (GTE) is a complex polyphenol that has been used in HDSs ubiquitously. Importantly, GTE has been implicated in more than 60 cases of human hepatotoxicity. The precise mechanism of injury due to GTE is conjectural, but likely is related to heightened oxidative stress induced by an overabundance of hydroxyl groups. The clinical picture of liver injury caused by GTE typically includes a very high alanine aminotransferase (ALT) concentration with jaundice, such as what may be seen with acute viral hepatitis. One of the most compelling studies linking GTE to liver injury was published by Wu et al.[7] In this study of 1021 women involved in a study of GTE as a preventative agent for the development of breast cancer, subjects were randomized to receive GTE 656 mg twice a day versus placebo. Women treated with GTE were seven times more likely to have ALT elevations. Even more compelling as proof of GTE being the cause for injury were cases in which liver injury resolved with cessation of GTE but recurred with its reinstitution.

In summary, HDSs are often used in the United States, and liver injury caused by supplements can lead to severe outcomes. An accurate diagnosis requires careful exclusion of other causes of liver injury; this process forms the foundation for structured causality assessment methods. But despite these instruments, the possibility of unlabeled ingredients confounds the accurate attribution of injury to any single ingredient. Finally, GTE is widely consumed and is now accepted as an agent with hepatotoxic potential. The exact mechanism, or a safe threshold dose, has not been determined.

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